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09/012,369	01/23/1998	BENJAMIN LEWIS MARGOLIS	231/198	2028

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EXAMINER	
HUNT, JENNIFER ELIZABETH	
ART UNIT	**PAPER NUMBER**
1642	25

DATE MAILED: 07/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/012,369	Marglis et al.
Examiner	**Art Unit**
Jennifer Hunt	1642

-- ***The MAILING DATE of this communication appears n the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 25, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26-32 and 35* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26-32 and 35* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. Acknowledgment is made of the cancellation of claims 33-34. Claims 26-32 and 35 are pending in the application and considered herein.

2. All rejections of claims 33 and 34 are withdrawn in light of the cancellation thereof.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Claim Rejections Maintained

4. The rejection of pending claims 26-32 and 35 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons set forth in the previous office action.

5. As set forth in the previous office action, the term "therapeutically effective amount" in pending claims 26-32 and 35 is a relative term which renders the claim indefinite. The term "therapeutically effective amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, it is not clear what therapeutic effect is being sought, and thus it cannot be determined at what point the therapy would be considered "effective".

Applicant argues that the specification at page 8, lines 8-12 defines the term "therapeutically effective amount," in regard to inhibiting cell growth or proliferation, and further that determination of effective amounts is well within the capability of those of ordinary skill in the art. Applicant's arguments filed 3-25-2002 have been fully considered but they are not persuasive.

With regard to the definition in the specification, this definition is a non-limiting definition, which provides only limited guidance as to what therapeutic effect might be sought, and which does not specify precisely what therapeutic effect is sought with regard to the claimed method, such that one of ordinary skill in the art could readily ascertain what therapeutic effect is sought. The guidance in general in the specification that "an amount which inhibits, to some extent, growth of cells causing or contributing to a cell proliferative disorder and brings about a therapeutic effect in a human" is not sufficient to determine a "therapeutically effective amount" because it is still not clear how much inhibition is required to "inhibit to some extent" and further it is not clear how to determine which cells are encompassed by the category of "causing or contributing to a cell proliferative disorder", and lastly, the definition in the specification requires bringing about a therapeutic effect in a human, and thus part of the definition of a therapeutic effect is the result of a therapeutic effect, which provides no further guidance as to what therapeutic effect is sought.

6. As set forth in the previous office action, pending claims 26-32 and 35 are unclear in the recitation of the term "agent". The metes and bounds of an "agent" cannot be determined. It is not clear what would be considered an agent and what would not.

Applicant argues that the term agent is defined throughout the specification, citing specific descriptions at page 6, lines 7-9, page 10, lines 3-15, particularly lines 12-15, and page 23, line 26- page 33, line 7. Applicant argues in general that an agent is defined as "able to modulate APB mediated activity between proteins, and thus alter signal transduction," and further that the claims recite that the agent must decrease the binding between an APB recognition and an APB domain." Applicant's arguments filed 3-25-2002 have been fully considered but they are not persuasive.

The specification and the claims provide only non-limiting, functional description of an agent, and thus provide no guidance as to the metes and bounds or structural properties of an "agent" absent that it exhibits a particular function. Further, the function asserted, that it mediates binding is unclear, in that it is not clear what activity an agent must posses to be considered to mediate binding; must it prevent binding, or could it decrease, or even increase binding affinity? Must it completely control binding or might it simply play a role in the control of binding activity?

7. The rejection of pending claims 26-32 and 35 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in the previous office action, factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to a method of altering signal transduction in an APB domain containing signal transduction pathway comprising administering to a patient a therapeutically effective amount of an agent which decreases binding between an APB recognition region in a first protein and an APB domain present in a second protein.

APB domain is broadly defined as having at least 20% sequence identity to the APB domain present in Shc (ie: AA's 46-209 of $p52^{shc}$) and "can" play a role in signal transduction. Thus the term "APB domain" encompasses a large number of proteins.

Further, the method is drawn to "altering" signal transduction, and thus encompasses both enhancing and decreasing signal transduction, as well as any other sort of "alteration".

Additionally, an "agent" is not defined in the specification and thus the scope of such cannot be determined.

Thus the claims are drawn to a method of determining how an "agent" which is not clearly defined "alters' (either increasing or decreasing or any other affect) signal transduction by binding to an "APB domain" (when APB domain encompasses an innumerable quantity of proteins).

The specification teaches that two specific regions of Shc (Shc 1-209 and Shc 46-209) (which would be considered APB domains) bind to phosphorylated EGFR, HER2/neu, and TrkA (which would be considered to contain APB recognition regions). The specification fails to teach any other "APB domains", nor does it provide guidance as to any other domains which would be expected to function as the exemplified embodiments do.

Prediction of how variations in protein sequence will affect function is complex and outside of the realm of routine experimentation as set forth below:

Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are

critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3).

Further, no other "APB recognition regions" are taught or suggested, absent the exemplified EGFR, HER2/neu, and TrkA. No "agent" is administered, and thus it is not clear how any agent would affect binding between an APB domain and an APB recognition region, nor is it clear if binding was affected, if the affect would be capable of altering signal transduction.

As set forth in previous Office Actions, there is insufficient evidence provided to support a role for APB binding in the mediation of signal transduction, because there is no objective evidence that disruption of APB binding to EGFR, HER2/neu, TrkA, or any other protein which contains an "APB recognition region" results in the predictable alteration of signal transduction. No therapeutic agents which promote or disrupt such binding are provided. Further, it is not disclosed what region of the EGRF, HER2/neu and TrkA receptors are bound. Neither is the role of binding in signal transduction suggested or provided. In fact, the specification teaches that it is art-known that specific binding is determined by SH2 domains, but that the physiological role of APB binding is unknown (see page 57 and page 64 of the specification). Further, the specification warns that the data presented must be approached with caution and that the interactions seen instantly, involving protein fragments may not be representative of the full length situation (see page 63 of the specification).

Further, the claims encompass the experimental and unpredictable field of in vivo therapy for mammals. An article by *Dermer (BIO/TECHNOLOGY, Vol 12, page 320, 03/1994*) is cited in order to establish the general state of the art and the level of predictability of in vivo therapy.

Dermer teaches that "What is significant in culture, for example immunotherapy's killing power or the transformation of 3T3 cells by a mutated proto-oncogene, simply does not have the same significance for cells in vivo."

Those of skill in the art recognize that in vitro assays are generally useful to screen the effects of agents on target cells. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo experiment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays to mammal or human therapeutic with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state.

Further a therapeutic agent must accomplish several tasks to be effective: it must be delivered into circulation and interact at the proper site of action, and it must do so at a therapeutic concentration and remain effective for a sufficient period of time. In vitro assays cannot duplicate the complex conditions of in vivo therapy. In assays, the agent is in contact with the cells during the entire exposure period, whereas in the case of in vivo therapy, exposure at the target site may be delayed or insufficient. Discussing agents used to treat cancer, *Jain, Science Vol 271, 23 February 1996, pages 1079-1080* states that "Because of their potent effect on cancer cells in vitro and in some in vivo tumor systems, these agents have been heralded as breakthrough drugs, or "magic bullets" and have been enthusiastically accepted as such by policy makers, investors, and the general public. Although the potential for using these agents in cancer therapy is great and almost certainly justified, clinical results to date have not met the high

expectations extrapolated from carefully planned and performed preclinical studies." *Jain , R. K. (Cancer and Metastasis Reviews, 9:753-266, 1990)* teaches that the efficacy in cancer treatment of novel therapeutic agents such as monoclonal antibodies, cytokines and effectors cells has been limited by their inability to reach their target *in vivo* in adequate quantities. Three physiological factors responsible for the poor localization of macromolecules in tumors have been identified: (I) heterogeneous blood supply, (ii) elevated interstitial pressure which lowers fluid extravasation, and (iii) large transport distances in the interstitium. Furthermore, the average vascular surface area decreases with tumor growth, hence reducing transvascular exchange in large tumors compared to smaller tumors. The molecule may also bind non-specifically to proteins or other tissue components; bind specifically to the target and or be metabolized, which further lowers the effective diffusion rate by reducing the amount of mobile molecule. Finally, although the effector cells are capable of active migration, peculiarities of the tumor vasculature and interstitium may be also responsible for poor delivery.

Therefore one of skill in the art would conclude that in vivo therapy of signal transduction disorders including cancer is an unpredictable and complex art and that in vitro tests are not sufficient to enable in vivo treatments.

Further, the specification does not disclose treatment of any cells, but rather the speculative possibility that there might be a treatment which could affect binding activity which was only tested in vitro.

Therefor for reasons set forth above, and in previous Office Actions, one of skill in the art would not be enabled to practice the invention as claimed.

(1) Applicant argues that the APB domain is now limited to APB domains which share at least 80% sequence similarity or at least 75% sequence identity with the APB domain present in Shc. (2) Applicant next argues that since the APB domain has been identified as part of a know protein, Shc, that other proteins having this domain can be readily identified by one of ordinary skill in the art. (3) Applicant next cites a section of the specification which described potential binding assays which can be used to identify compounds which can be used in the methods of the invention. (4) Applicant next argues that the APB domain is in the amino terminus of Shc which is implicated in signal transduction, is distinct from SH2, and which represents a newly elucidated mechanism of protein interaction with growth factor receptors and other tyrosine phosphorylated proteins. (5) Applicant last argues that the in vitro data provided in the specification, and further the in vitro data provided post filing supports the claims as they encompass in vivo treatment. Applicant's arguments filed 3-25-2002 have been fully considered but they are not persuasive.

(1) While the claims are not limited to APB domains which share at least 80% sequence similarity or at least 75% sequence identity with the APB domain present in Shc, they are still broadly drawn, particularly in light of the complexity of amino acid substitutions set forth above. (2) Further, the identification of a region which might be contained within other proteins does not provide support for any protein which might contain that domain, including those proteins which

are yet undiscovered. There must be a reasonable correlation between the invention which is discovered, and the patent protection which is sought. To seek out protection for any protein which might encompass similar structure or properties represents an invitation to experiment, and is not commensurate in scope with what was disclosed. (3) The ability to screen compounds for a desired activity is an invitation to experiment. There must be a reasonable correlation so that one of skill in the art would be readily able to identify compounds which meet the limitations of the claims. In the instant case, no specific structure is set forth, and no guidance is given as to which specific compounds might meet the limitations and which would not. (4) As set forth in previous Office Actions, there is insufficient evidence provided to support a role for APB binding in the mediation of signal transduction, because there is no objective evidence that disruption of APB binding to EGFR, HER2/neu, TrkA, or any other protein which contains an "APB recognition region" results in the predictable alteration of signal transduction. No therapeutic agents which promote or disrupt such binding are provided. Further, it is not disclosed what region of the EGRF, HER2/neu and TrkA receptors are bound. Neither is the role of binding in signal transduction suggested or provided. In fact, the specification teaches that it is art-known that specific binding is determined by SH2 domains, but that the physiological role of APB binding is unknown (see page 57 and page 64 of the specification). Further, the specification warns that the data presented must be approached with caution and that the interactions seen instantly, involving protein fragments may not be representative of the full length situation (see page 63 of the specification). Applicants arguments do not provide further

evidence of such. (5) As set forth previously, is known in the art that the simplicity of the in vitro experiment does not correlate the complexity of an in vivo therapeutic effect. Submission of further in vitro data and mechanisms of action do not address the problems of targeting, therapeutic dosages at appropriate sites, or maintained effect in the environment of other physiological effects which plague in vivo therapy. Further, since the claims, read in light of the specification encompass clinical therapy of humans, then a reasonable correlation must exist between that which is claimed, and that which is taught in the specification.

New Grounds of Rejection

8. Claims 26-32, and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims now recite the limitation "wherein said APB domain shares at least 80% sequence similarity or at least 75% sequence identity with the APB domain present in Shc". The specification does not support this limitation. At page 25, lines 1-6, cited for support, the specification recites that "the APB domain has at least 80% sequence identity to the APB domain present in Shc, or at least 75% sequence similarity to the APB domain in Shc" which is of different scope from that which is instantly claimed.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

June 30, 2002

SHEELA HUFF
PRIMARY EXAMINER